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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,697	08/05/2003	Pablo Umana	1975.0010005/TJS/AWL	5455
26111	7590	04/11/2006	EXAMINER	
STERNE, KESSLER, GOLDSTEIN & FOX PLLC 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005			GUZO, DAVID	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,697	UMANA ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 86-162 is/are pending in the application.
- 4a) Of the above claim(s) 133-157, 161 and 162 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 86-132 and 158-160 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/28/04</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Election/Restriction

Applicant's election with traverse of Group I, Claims 86-132 and 158-160 in the reply filed on 12/30/05 is acknowledged. The traversal is on the ground(s) that a search of the art for Group I would likely find art on the claims of Group II and *vice versa* because both groups share the important feature of antibodies having increased Fc mediated cellular cytotoxicity and Fc receptor binding. This is not found persuasive because the claimed methods of lysing target cells reads on lysing cells *in vitro* and *in vivo*. A complete search of the claims in Group II would involve a search of the therapeutic arts concerning therapeutic use of antibodies to kill cancer cells *in vivo*. This type of search would not be involved in a search of the elected method of producing an antibody with increased Fc mediated cellular cytotoxicity and hence said search would be burdensome.

It is noted that claim 158 was erroneously included in Group II. It should have been included in elected Group I. It will be examined in Group I.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Priority for claims 90, 94, 96, 97, 101, 106-108, 114, 127 and 128 is granted back to the filing date of the instant application (8/5/2003) as support for the claimed invention is not found in parent applications 09/294,584 and 60/082,581. Priority for the

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remaining claims is granted back to the filing date of the 60/082,581 application (4/20/98).

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 86-88, 90-91, 95-98, 100, 102-103, 105-132, 158-160 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a recombinant antibody having increased Fc mediated cellular cytotoxicity, comprising providing CHO cells expressing a recombinant antibody comprising an Fc region containing N-linked oligosaccharides, glycoengineering said CHO cells so as to express the glycosyltransferase $\beta(1,4)$ -N-acetylglucosaminyltransferase III (GnT III), culturing said cells under conditions which permit production of the recombinant antibody, isolating the antibody with increased ADCC, does not reasonably provide enablement for the above method using any host cell expressing any glycoprotein-modifying glycosyltransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information

known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Unpredictability of the art. The art here involves glycoengineering recombinant antibodies so as to increase Fc-mediated cellular cytotoxicity (ADCC). This glycoengineering involves altering at least one glycoprotein-modifying glycosyltransferase in the cell which produces the antibody so as to produce an antibody with increased ADCC. Applicants present two examples of this using recombinant CHO cells (transformed with expression constructs inducibly expressing GnT III) that produce either the chCE7 antibody or the C2B8 antibody, wherein said antibodies exhibit altered glycosylation patterns and increased ADCC. The increased ADCC activity is presumed to be due to an increase in the proportion of antibodies having bisected, hybrid glycans as a result of expression of the GnT III gene.

However, the art in this field is unpredictable. In the instant specification, applicants utilize CHO cells for glycoengineering. CHO cells were chosen because they lack expression of an endogenous GnT III gene and produce oligosaccharides with no bisecting *N*-acetylglucosamine (GlcNAc) residues. Applicants transformed the CHO cells with an expression vector capable of inducibly expressing GnT III and with vectors expressing the chCE7 or C2B8 antibodies. While the theory is that increased levels of

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bisected (hybrid) GlcNAc residues (resulting from increased expression of the GnT III gene) present on the antibodies enhances ADCC, it is noted that applicants found that the highest levels of GnT III expression led to reduced ADCC activity of the chCE7 antibody while the highest levels of GnT III led to the highest level of ADCC activity for the C2B8 antibody. Therefore, a higher ratio of bisected, hybrid to bisected, complex glycans does not always correlate with increased ADCC and may even lead to decreased ADCC. The effects of expression of other glycoprotein-modifying glycosyltransferases (i.e. α -mannosidase II, α -1,6-fucosyltransferase, etc.) on increasing ADCC activity is unknown. Furthermore, the selection of the cells used to produce the glycoengineered antibodies adds an unpredictable element. Raju et al. (Glycobiology, 2000, Vol. 10, No. 5, pp. 477-486) notes that different cell lines have different glycosylation machinery and that glycosylation of recombinant antibodies produced in different cell lines from different species will likely be significantly different. Applicants provide no teaching on what additional cell lines (except to recite three or four cell lines which may be tried) can be used to produce recombinant antibodies with enhanced ADCC and applicants provide no specific teachings on how the glycosylation machinery of said cells may be modified to enhance ADCC of antibodies produced in said cells.

It is also noted that the significance of bisecting GlcNAc in enhancing ADCC is controversial. For example, Shinkawa et al. (J. Biol. Chem., 2003, Vol. 278, No. 5, pp. 3466-3473) indicates that the absence of fucose in oligosaccharides on IgG1 molecules had a much more significant effect on enhancing ADCC than the presence of bisected

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GlcNAc and that an increased effect of bisecting GlcNAc was only observed in highly fucosylated IgG1 with a high content of bisecting GlcNAc. This is in contrast with results presented by applicants with the chCE7 antibody where high levels of bisecting GlcNAc actually reduced ADCC. Therefore, it is unpredictable as to what level of bisecting GlcNAc will increase ADCC of any given antibody and indeed, each antibody would have to be tested empirically to determine whether the claimed bisected glycan ratio increases or decreases ADCC. Also, with regard to the host cell used, it is unpredictable whether any particular change to the glycosylation machinery of said cell will have any effect on the glycosylation of any particular antibody so as to increase the ADCC activity of said antibody.

2) State of the art. The state of the art regarding increasing the ADCC of a given antibody by a higher ratio of bisected, hybrid to bisected, complex glycans is undeveloped. As explained above, each antibody would have to be tested empirically to determine whether the claimed bisected glycan ratio increases or decreases ADCC.

3) Number of working examples. Applicants present two examples of antibodies with enhanced ADCC produced in CHO cells transformed with a tet regulated GnT III gene.

4) Amount of guidance. Aside from the two examples, applicants provide no direction for selecting cell lines, glycoengineering said cells so as to increase the ADCC for any given antibody by increasing the ratio of bisected, hybrid to bisected, complex glycans. The relevant art (cited above) teaches that ADCC is not associated with this ratio, and that antibodies bearing this ratio may or may not have increased ADCC. The

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specification requires the skilled artisan to practice trial and error experimentation with different antibodies, cell lines, and glycoprotein modifying glycosyltransferases to determine which will yield antibodies with enhanced ADCC activity.

5) Scope of the invention. The scope of the invention is broad with the broadest claims encompassing producing any antibody having increased ADCC by providing any host cell from any species, glycoengineering said host cell to alter the activity of any of the glycoprotein modifying glycosyltransferases and culturing the cell so as to produce the modified antibody.

6) Nature of the invention. The invention involves a complex, unpredictable, recombinant method for glycoengineering host cells so as to produce antibodies with enhanced ADCC.

7) Level of skill in the art. The level of skill in the art is high. However, given the unpredictability of the art, the poorly developed nature of the art, the lack of guidance and the broad scope of the invention, it must be considered that the skilled artisan would have had to have conducted essentially trial and error experimentation in order to practice the claimed invention.

Given the above analysis of the factors that the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Claims 89, 92-94, 99, 101 and 104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The subject matter of the rejected claims is directed to a method for producing a recombinant antibody having increased ADCC comprising glycoengineering a host cell so as to alter the level of activity of a non-GnT III enzyme, such as α -mannosidase II, α -1,6-fucosyltransferase, etc. These claims are not enabled for reasons outlined in the above 35 USC 112, 1st paragraph (scope of enablement rejection) and will not be repeated here.

Claims 86-132 and 158-160 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a method for producing antibodies having increased ADCC, said method comprising using glycoengineered host cells and antibodies. Applicants disclose CHO cells which inducibly express exogenous GnT III wherein said cells were engineered to produce two different antibodies which have increased ADCC. The claims read on a genus of methods where any cell can be used and any activity of any

glycoprotein-modifying glycosyltransferase in said cell can be altered so as to produce any antibody with enhanced ADCC.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

In the instant case, applicants only disclose CHO cells transfected with GnT III and chCE7 or C2B8 antibody expression vectors. These cells can be used to produce the chCE7 and C2B8 antibodies, respectively, that have increased ADCC, likely due to an increase in the ratio of bisected, hybrid to bisected, complex glycans. Neither applicants nor the prior art disclose additional host cells capable of increasing the ADCC of any antibody by glycoengineering the host cell so as to alter one or more glycosyltransferases in said cell. As discussed in the enablement rejection above, it is unpredictable whether altering the activity of any glycosyltransferase (other than GnT III in CHO cells) can result in increased ADCC of a given antibody. How then can there be any basis for the skilled artisan to envision any embodiments of the claimed invention other than those instantly disclosed? Applicants claim methods to produce antibodies with increased ADCC by glycoengineering by function only, without a correlation between structure and function. For example, applicants present no written description

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of any non-CHO cells or cell lines which have been glycoengineered so as to express an altered glycosyltransferase which results in production of an antibody with enhanced ADCC. Neither applicants nor the prior art disclose any non-GnT III glycosyltransferase which has been engineered to increase the ADCC of any antibody in any cell. Given the ambiguity in what oligosaccharide features are actually important in determining ADCC, the skilled artisan would not be able to envision additional embodiments of the claimed invention. Also, the diversity of the host cells and antibodies involved and lack of disclosure regarding which antibodies, cell lines, and glycosyltransferase levels should be used, would likewise render the skilled artisan unable to envision additional embodiments of the claimed invention. It must be considered therefore, that the disclosure of two examples of antibodies having enhanced ADCC prepared using CHO cells is not a sufficient number to describe the claimed genus.

Claims 90, 94, 96, 97, 101, 108-109, 114, 122, 127 and 128 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a method for producing a recombinant antibody having increased ADCC comprising altering (i.e. decreasing) the activity of core α -1,6-fucosyltransferase or modifying the activity of the three enzymes GnT III, α -

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mannosidase II and $\beta(1,4)$ -N-acetylglucosaminyltransferase. There is no support for these limitations in the application as originally filed. Applicants claim a method for producing a recombinant antibody having increased ADCC wherein said antibody has an increased proportion of nonfucosylated oligosaccharides or wherein the predominant N-linked oligosaccharide is nonfucosylated or wherein the predominant N-linked oligosaccharide in the Fc region is not a high-mannose structure. There is no support for these broad limitations in the application as originally filed. This is a NEW MATTER rejection.

Obviousness Type Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 86-88, 90-91, 97-98, 102-103, 106-107, 110-113, 120-121, 123-125, 129, 131-132 and 159-160 are rejected on the ground of nonstatutory obviousness-type

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double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,602,684 (hereafter the '684 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite the same methods for producing recombinant antibodies with increased ADCC. The instant claims are generic with regard to altering the activity of at least one glycoprotein-modifying glycosyltransferase or recite GnT III, as is claimed in the '684 patent. With regard to the species of cell used (i.e. CHO cells, SP2/0 cells, BHK cells, etc.), the type of recombinant antibody produced (therapeutic, humanized, etc.), it is noted that the specification of the '684 patent (see for example columns 8-9) recites these as preferred species of cells to use or antibodies to produce.

Claims 86-88, 90-91, 97-98, 102-103, 106-107, 110-113, 120-121, 123-125, 129, 131-132 and 159-160 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 11/199,232. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite the same methods for producing recombinant antibodies with increased ADCC. The instant claims are generic with regard to altering the activity of at least one glycoprotein-modifying glycosyltransferase or recite GnT III, as is claimed in the '232 application. With regard to the species of cell used (i.e. CHO cells, SP2/0 cells, BHK cells, etc.), the type of recombinant antibody produced (therapeutic, humanized, etc.), it is noted that

the claims of the '232 patent specifically recite these as preferred species of cells to use or antibodies to produce.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claim 97 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 97 is broader than the claims from which it depends because it recites that the activity is expression of at least one glycoprotein-modifying glycosyltransferase; however, claim 97 is dependent on claim 90 which recites that the glycoprotein-modifying glycosyltransferase is **selected from a group of five specific glycosyltransferases**.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Applicants, in an Application Data Sheet filed 8/5/03 indicate that inventor James E. Bailey is deceased. Where an inventor is deceased or legally incapacitated, an Oath or

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Declaration in accordance with the provisions of 37 CFR 1.42 or 1.43 must be provided
(See also 37 CFR 1.497(b) and MPEP 409.01 and 409.02).

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
March 30, 2006


DAVID GUZO
PRIMARY EXAMINER